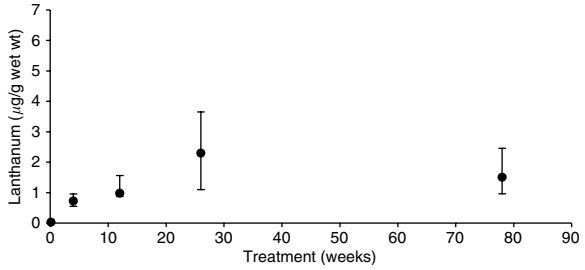

Figure 1 | Long-term liver lanthanum exposure. Liver lanthanum concentrations in rats treated for 1 day, or 4, 12, 26, or 78 weeks with 1500–2000 mg/kg lanthanum carbonate, 13–17 times the human dose of 3 g/day of elemental lanthanum. Values are the median and 25th/75th percentiles, $n = 4$–12 rats per time point. Data on file at Shire Pharmaceuticals Inc., in preparation for publication.

appear to be little likelihood that the small quantities of lanthanum absorbed with therapeutic doses of lanthanum carbonate will lead to lysosomal overload and toxicity. Extensive preclinical and clinical safety testing supports this conclusion.

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Response to 'Enlightenment on liver lanthanum exposure'

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In a letter to the editor, Damment[1] from Shire Pharmaceuticals has questioned the interpretation of the results from our recently published study in this journal.[2] We looked at the tissue accumulation of lanthanum in kidney, bone, and liver from normal and uremic lanthanum-treated rats. In Damment's letter, he suggests that the only appropriate comparison is the one between the lanthanum-treated normal and lanthanum-treated uremic rats. When looking at tissue accumulation, the appropriate control for lanthanum-treated uremic rats is untreated uremic rats. When we made this comparison, we demonstrated a progressive accumulation of lanthanum in liver over the entire course of the study. We also observed that uremia enhances the accumulation of lanthanum as has been shown by other investigators.[3,4] In his letter, Damment includes a graph showing that lanthanum accumulation reaches steady-state conditions in longer term studies. This study, however, was not performed in uremic rats, but in normal animals. As with Damment's study, we also saw that lanthanum accumulation in liver begin to plateau in lanthanum-treated normal rats.[2] Lanthanum, however, will not be prescribed to normal individuals; thus, these results have no relevance for hemodialysis patients. On the other hand, Bervoets *et al.*[3] showed significantly greater gastrointestinal absorption of lanthanum in renal failure. This explains why we see a greater and progressive accumulation of lanthanum in the uremic state. Initial concern for lanthanum use had centered around its potential effects on bone and brain, as these were the tissues adversely affected by aluminum-containing phosphate binders.[5] We state in our paper that lanthanum likely has no effect on either of these tissues or for that matter, kidney. Given the experience with aluminum-containing phosphate binders, we must be certain that treatments designed to benefit our patients will not, in fact, harm them. The jury is still out.

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Downloadable computer models for maintenance but not acute renal replacement therapy

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To the Editor: The hemodialysis clearance calculators developed by Walther *et al.*[1] are a commendable initiative. However, we wish to draw attention to their limitations for modelling acute renal replacement therapy in the intensive care unit. Like Michael's equation, Dr Addis' hemodialyzer clearance (K_d) calculator assumes a fixed configuration for blood flow (QB) and dialysate flow (QD) within the

hemodialyzer, and a constant hemodialyzer mass transfer coefficient (KoA) over a wide range of hemodialysis operating conditions.[2] When QB and QD are low, however, mismatch of these flows within the hemodialyzer creates a shunt in which no solute transfer occurs. In a previous study of nine patients during sustained low-efficiency dialysis, QB of 200 ml/min and QD of 100 ml/min were used with a 1.8 m^2 polysufone low-flux hemodialyzer.[3] Measured K_d for urea by direct dialysis quantification averaged 77.9 ml/min, as opposed to ~100 ml/min predicted by both Michael's equation and Dr Addis' calculator. Hemodialyzer KoA during sustained low-efficiency dialysis averaged only 203.2 ml/min, much lower than the manufacturer's value. Such errors in calculated K_d are important as they lead directly to misleading solute time–concentration profiles in Dr Conlon's dialysis simulation spreadsheet, which does not iteratively recalculate solute generation rate and volume of distribution to offset input error.[4] Finally, critically ill patients with acute kidney injury are seldom in solute steady state;[5] this assumption underpins Dr Conlon's dialysis simulation spreadsheet and is unrealistic. In summary, the calculators by Walther *et al.*[1] are useful for stable patients with end-stage kidney disease, but are less suited for modelling acute renal replacement therapy in the intensive care unit.

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Response to 'Downloadable computer models for maintenance but not acute renal replacement therapy'

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We are grateful to Drs Marshall and Golper[1] for pointing out that when flows are low, dialyzers may not achieve the clearance rates predicted from values for K_oA that are derived from clearances measured at higher flows. We should have noted in addition that clearances *in vivo* are often lower than those predicted from manufacturers' K_oA values, which are usually derived from clearance experiments performed with saline solutions. An even greater problem is that K_oA values are usually available only for urea, creatinine, and vitamin B_{12}, and must be guessed at for other solutes of interest. We disagree somewhat with Drs Marshall and Golper about the application of the models to acute renal failure. We should emphasize that it is only the downloadable format, and not the theoretical content, of our models that is new. Like other theoretical models, they can predict plasma solute concentrations only when solute production rates, solute distribution volumes, and residual renal function are specified, and these latter parameters are both variable and hard to estimate in acutely ill patients. But we think that the models can still be useful in helping nephrologists to think about solutes other than urea. An example may be provided by the description of sustained low-efficiency dialysis with Q_B of 200 ml/min and Q_D of 100 ml/min to which Marshall and Golper refer.[2] If urea is the only solute considered, the predicted clearance is not much different for Q_B of 200 ml/min and Q_D of 100 ml/min as compared to Q_B of 100 ml/min and Q_D of 200 ml/min. But the models predict that the clearance of solutes, which bind to plasma proteins, will be higher using Q_B of 100 ml/min and Q_D of 200 ml/min.[3] We think it is wrong to assume that all uremic toxins behave like urea, and that modeling the effect of renal replacement therapies on other classes of solutes may thus have some value.

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Hardy–Weinberg equilibrium and control subjects

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To the Editor: Consider a gene locus with two alleles, 'A' and 'a'. The frequency of allele 'A' will be designated by p and that of allele 'a' by q. Hardy and Weinberg showed that in a very large population with random mating, the frequencies of AA, Aa, and aa genotypes are p^2, $2pq$, and q^2, respectively. The